

Remarks

I. Support for Amendments

Support for the foregoing amendments to the claims can be found in the specification as originally filed. Specifically, support for the amendments to claims 1 and 33, and for new claims 38-41, can be found in the specification at page 7, lines 10-14; at page 11, lines 24-26; throughout the Examples; and in the drawings at Figures 2-4. Accordingly, no new matter is added by these amendments, and their entry and consideration are respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 1 and 33 are sought to be amended and new claims 38-41 are sought to be entered. Upon entry of these amendments, claims 1-9, 11-28 and 33-41 are pending in the application, with claims 1, 33 and 37 being the independent claims.

III. Summary of the Office Action

In the Office Action dated December 3, 2002, the Examiner has withdrawn claims 11-16 from consideration, has objected to the Information Disclosure Statement filed on November 12, 2002, and has made six rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

IV. Election/Restrictions

As an initial matter, Applicants note that the Examiner has again indicated on the Office Action Summary (Form PTO-326) attached to Paper No. 24 that claims 11-16 are withdrawn from consideration. This statement is also made in the Office Action at page 2, wherein the Examiner contends that claims 11-16 are "drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6." Paper No. 24 at page 2, lines 13-15 (emphasis in original). Applicants respectfully disagree with these contentions.

Applicants note that in the restriction requirement issued in Paper No. 6 (at page 2), to which the Examiner refers in the present Office Action, claims 11-16 were included in restriction group I (which comprised claims 1-28 and 33). Group I was elected by Applicants without traverse via telephone (*see* Paper No. 6 at page 4, lines 1-3) and in writing (*see* Amendment and Response filed October 4, 2001, at page 2). It is further noted that claims 11-16 were considered by the Examiner as being drawn to a non-elected species, the species of mammalian uricase having been elected both via telephone (*see* Paper No. 6 at page 4, line 3) and in writing (*see* Amendment and Response filed October 4, 2001, at page 2). Thus, contrary to the Examiner's contentions, claims 11-16 were *not* part of a non-elected restriction group under 37 C.F.R. § 1.142, but instead represent non-elected species under 37 C.F.R. § 1.146. Applicants respectfully assert that generic claim 1 and dependent claim 2 (encompassing the elected species, mammalian uricase) are allowable, in view of the remarks

contained herein. Hence, it is respectfully requested that claims 11-16 be rejoined and examined with the remaining claims in restriction group I, and that these claims be allowed. *See* 37 C.F.R. § 1.141(a) and 1.146, and MPEP § 809.02(c)(B).

V. The Information Disclosure Statement

In the Office Action at page 3, the Examiner has objected to the Information Disclosure Statement filed November 12, 2002 ("the IDS"), for allegedly failing to comply with 37 C.F.R. § 1.98(a)(3) by not including a concise explanation of the relevance of the non-English language documents cited thereon, DD 279 486 A1 (Doc. No. AM1) and JP 09154581 (Doc. No. AO1). Applicants respectfully disagree with these contentions.

The concise explanation of the relevance of Doc. Nos. AM1 and AO1 that is required under 37 C.F.R. § 1.98(a)(3) was, in fact, provided in the IDS. Specifically, the following statements were included in the IDS:

In accordance with 37 C.F.R. § 1.98(a)(3), Applicants' undersigned representative submits the following, in regards to non-English language documents AM1 and AO1 cited on Form PTO 1449:

Document **AM1**, East German Patent No. DD 279 486 A1, is in the German language. An unverified English language abstract of document AM1 is attached as document **AR18**.

Document **AO1**, Japanese Patent No. JP 09154581, is in the Japanese language. An unverified English language abstract of document AO1 is attached as document **AS18**.

IDS at pages 1-2. Hence, the required statements of the relevance of the referenced documents are provided by citation of English-language abstracts for the Doc. Nos. AM1 and

AO1, cited as Doc. Nos. AR18 and AS18 on the same Form PTO-1449. These submissions satisfy 37 C.F.R. § 1.98(a)(3), since “[s]ubmission of an English language abstract of a reference may fulfill the requirement for a concise explanation.” MPEP § 609 III A(3), at page 600-122, col. 2 (August 2001). In fact, the Examiner has initialed the Form PTO-1449 next to Doc. Nos. AR18 and AS18 (*see* initialed form PTO-1449 attached to Paper No. 24, at page 8), indicating that these concise explanations of the relevance of Doc. Nos. AM1 and AO1, in the form of English-language abstracts, have been considered by the Examiner. Hence, the Examiner’s refusal to consider Doc. Nos. AM1 and AO1, despite the on-the-record consideration of the separately cited English language abstracts for these references which fulfill the requirements of 37 C.F.R. § 1.98(a)(3), is contrary to the clear guidance of the MPEP on this issue.

Accordingly, Applicants respectfully submit that the IDS submitted on November 12, 2002, fully complies with the requirements of 37 C.F.R. § 1.98(a)(3). It is therefore respectfully requested that the Examiner consider Doc. Nos. AM1 and AO1. It is further requested that the Examiner indicate on the record that these documents have been considered, and that an initialed Form PTO-1449 or a Form PTO-892 citing these documents and evidencing their consideration on the record be included with the next communication from the Examiner to Applicants.

VI. The Rejection Under 35 U.S.C. § 102(b) Over Aleman Is Traversed

In the Office Action at pages 3-4, the Examiner has rejected claims 1, 4, 6 and 33 under 35 U.S.C. § 102(b) as being anticipated by Aleman *et al.*, U.S. Patent No. 5,811,096 (Doc. No. A1 on the Form PTO-892 attached to Paper No. 24; hereinafter “Aleman”). Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) (“To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.”). These standards are not met by the disclosure of Aleman.

Independent claims 1 and 33 are drawn to purified uricases that are substantially free of aggregates larger than octamers. In contrast, there is absolutely no evidence that the uricase preparations disclosed in Aleman are substantially free of aggregates larger than octamers. Indeed, Aleman is silent on this issue, and the Examiner has pointed to no explicit statement in Aleman that the uricase disclosed therein is substantially free of octamers. Thus, there is no express disclosure in Aleman of the subject matter of claims 1, 4, 6 and 33.

Applicants note, however, that in making this rejection, the Examiner apparently is of the opinion that this reference *inherently* discloses the invention. Specifically, the Examiner contends that “[i]t can be construed that Aleman et al teach an uricase [sic] substantially free of aggregates larger than octamers” Paper No. 24 at page 3, final paragraph, lines 4-5. Applicants respectfully disagree with these contentions.

Applicants submit that it is unclear upon what disclosure the Examiner is relying in “construing” that Aleman discloses purified uricase substantially free of aggregates larger than octamers. The portion of Aleman cited by the Examiner in making this rejection simply states that solutions of uricase in the presence of Polysorbate 80 or Poloxamer 188 exhibit reduced turbidity (*i.e.*, reduced aggregation) (*see* Aleman, Figs. 1-2; col. 5, lines 1-9; and claims 1-23). However, this disclosure says absolutely *nothing* about the size of aggregates present in those solutions, or whether the solutions are substantially free of aggregates larger than octamers. In fact, the use of turbidity measurements and the description of the uricase solutions in Aleman as “clear . . . after vigorous stirring,” Aleman at col. 2, lines 35-36, only indicates that Aleman *et al.* were concerned about *macroscopic*, *i.e.*, visible, aggregation, rather than the submicroscopic aggregation that the present invention addresses. As one of ordinary skill would readily appreciate, and in Applicants’ experience, solutions of uricase that contain aggregates larger than octamers can appear to be visibly clear. To demonstrate this point, the Examiner is referred to the figure displaying the chromatograms of three uricase preparations, attached hereto as Exhibit A. This figure represents plots of light absorbance at 214 nm (a measure of protein content) vs. retention time on chromatographic columns used to assess the

aggregation state of preparations of soybean uricase, a fraction (Fraction 7) of soybean uricase, and uricase from *Candida* spp. Importantly, each of these preparations was "clear after stirring" -- *i.e.*, they did not demonstrate visible turbidity. However, as can be readily seen from the chromatograms, these solutions each contained 14%-26% of their total protein in the form of aggregates larger than octamers (*viz.*, 14-16% for soybean uricase; 25-26% for soybean uricase fraction 7; and 19% for *Candida* uricase). Thus, each of these solutions would be considered to be "clear . . . after vigorous stirring," despite containing significant amounts of aggregates larger than octamers. Moreover, such clear solutions would exhibit reduced turbidity, since by definition turbidity is itself dependent upon the presence of *macroscopic* aggregates in a solution and is affected less, if at all, by the presence of *microscopic* aggregates (such as aggregates larger than octamers, some of which are microscopic). Hence, as one of ordinary skill would understand, visibly clear uricase solutions demonstrating reduced turbidity, such as those disclosed in Aleman, could (and likely *would*) nonetheless contain aggregates larger than octamers. Therefore, there is absolutely no basis for the contention that the presently claimed uricases are inherently disclosed in Aleman.

The Examiner is also reminded that "[i]n order for a disclosure to be inherent . . . the missing descriptive matter must necessarily be present in the [cited reference] such that one skilled in the art would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). Moreover, to rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior

art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). That is, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). These requirements are not met by the disclosure of Aleman.

As noted above, the Examiner has pointed to no disclosure in Aleman that is "necessarily present" such that it would be recognized by one of ordinary skill as disclosing uricase preparations that are substantially free of aggregates larger than octamers. Thus, the *Tronzo* standard is not met by the disclosure of Aleman.

As also discussed above, there is no reason to assume that just because a given uricase solution is reduced in turbidity or "clear," it is necessarily substantially free of aggregates larger than octamers. Simply because a given polymer may "reduce the degree of aggregation of urate oxidase in solution by as much as three fold," Paper No. 24 at page 3, does not *a priori* mean that the solution is substantially free of uricase aggregates larger than octamers as suggested by the Examiner. Hence, the Examiner has pointed to no disclosure in Aleman, and has provided no sound scientific reasoning, to support the notion that the missing disclosure in Aleman "necessarily flows" from what *is* disclosed in this reference. Thus, the *Levy* standard is not met by the disclosure of Aleman.

Finally, one of ordinary skill reading Aleman could find no disclosure indicating that it was even possible, let alone probable, that uricases that were substantially free of aggregates

larger than octamers could be obtained using the methods of Aleman. Thus, the *Continental Can* standard is not met by the disclosure of Aleman.

Accordingly, Aleman does not meet the requirements for inherent disclosure of the claimed invention under *Tronzo, Levy* and *Continental Can*, satisfaction of all of which are required. Hence, the Examiner's attempted reliance upon inherent anticipation in the present case is factually and legally unfounded.

Finally, the Examiner contends that "the teachings of Meredith anticipate claims 1, 4, 6 and 33." Paper No. 24 at page 4, lines 1-2. The identity of "Meredith" is unclear to Applicants, since no reference naming a "Meredith" as a first author or first inventor is of record in the present application. Applicants presume that this citation is in error, and that "Aleman" was intended instead of "Meredith" in this statement in the Office Action. Clarification of this issue on the record is respectfully requested.

In view of the foregoing remarks, Applicants respectfully assert that Aleman does not expressly or inherently disclose every element of the invention as claimed. Hence, reconsideration and withdrawal of the rejection of claims 1, 4, 6 and 33 under 35 U.S.C. § 102(b) over Aleman are respectfully requested.

VII. *The First Rejection Under 35 U.S.C. § 103(a) Over Aleman and Wu Is Traversed*

In the Office Action at pages 4-5, the Examiner has rejected claims 1-5 and 33-34 under 35 U.S.C. § 103(a) as being obvious over Aleman in view of Wu *et al.*, *Proc. Natl. Acad. Sci. USA* 86:9412-9416 (1989) (of record in Applicants' Information Disclosure

Statement filed January 25, 2001; hereinafter "Wu"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, a *prima facie* case of obviousness has not been established.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Aleman. Contrary to the Examiner's conclusory statement in the last sentence on page 4 of Paper No. 24, Aleman does not disclose, suggest, or otherwise contemplate the production of purified uricase that is substantially free of aggregates larger than octamers. Thus, Aleman is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Aleman are not cured by Wu. As the Examiner has acknowledged (*see* Paper No. 24 at page 8, second paragraph), Wu also does not disclose the

production of purified uricase that is substantially free of aggregates larger than octamers. Hence, there would have been no motivation to combine the disclosures of Aleman and Wu in the attempt to make and use the claimed uricase preparations.

As noted above, the Examiner appears to view the information that is explicitly missing from Aleman as inherent in that reference. As discussed above, however, Aleman does not meet the required standards for providing inherent disclosure of purified uricase substantially reduced in aggregates larger than octamers. In any event, Applicants wish to remind the Examiner that there is no such thing as "inherent obviousness," since inherence and obviousness are different legal concepts. *See In re Spormann*, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information "is not necessarily known . . . [and] Obviousness cannot be predicated on what is unknown." *Id.* Since the present rejection is based on obviousness, any contention by the Examiner that is based in any way on the possible presence of inherent knowledge in Aleman must necessarily fail.

Thus, neither Aleman nor Wu suggests that one of ordinary skill should combine the disclosures of these references in order to make and use the claimed invention, and one of ordinary skill would not otherwise have been motivated to combine their disclosures. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Moreover, to the extent that the Examiner is relying on any inherent disclosure in Aleman (which, as noted above, is not present therein), such inherency cannot be used in the attempt

to establish a *prima facie* case of obviousness. Accordingly, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-5 and 33-34 are not rendered obvious by Aleman and Wu, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

VIII. *The Second Rejection Under 35 U.S.C. § 103(a) Over Aleman and Wu Is Traversed*

In the Office Action at pages 5-6, the Examiner has rejected claims 1-7, 9 and 33 under 35 U.S.C. § 103(a) as being obvious over Aleman in view of Wu. Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosures of Aleman and Wu. These references do not disclose, suggest or otherwise contemplate the claimed invention, and one of ordinary skill would not otherwise have been motivated to combine their disclosures. Moreover, any attempt to rely on allegedly inherent disclosure in Aleman to support a rejection under 35 U.S.C. §103 is legally impermissible. Accordingly, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-7, 9 and 33 are not rendered obvious by Aleman and Wu, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

IX. The Rejection Under 35 U.S.C. § 103(a) Over Aleman and Delgado Is Traversed

In the Office Action at pages 6-7, the Examiner has rejected claims 1, 17-25 and 27-28 under 35 U.S.C. § 103(a) as being obvious over Aleman in view of Delgado *et al.*, U.S. Patent No. 5,880,255 (Doc. No. AB2, of record; hereinafter “Delgado”). Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Aleman. Aleman does not disclose, suggest, or otherwise contemplate the production of purified uricase that is substantially free of aggregates larger than octamers. Thus, Aleman is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Aleman are not cured by the disclosure of Delgado, which does not disclose the production of purified uricase that is substantially free of aggregates larger than octamers. Hence, there would have been no motivation to combine the disclosures of Aleman and Delgado in the attempt to make and use the claimed uricase preparations.

Thus, Aleman and Delgado, alone or in combination, do not disclose, suggest or otherwise contemplate the claimed invention, and one of ordinary skill would not otherwise have been motivated to combine their disclosures. Moreover, any attempt to rely on allegedly inherent disclosure in Aleman to support a rejection under 35 U.S.C. §103 is legally impermissible. Accordingly, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 1, 17-25 and 27-28 are not rendered obvious by Aleman and Delgado, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

X. *The Rejection Under 35 U.S.C. § 103(a) Over Wu and Ansaldi Is Traversed*

In the Office Action at pages 7-8, the Examiner has rejected claims 1 and 34 under 35 U.S.C. § 103(a) as being obvious over Wu in view of Ansaldi *et al.*, U.S. Patent Appl. Publication No. US 2002/0010319 A1 (Doc. B1 cited on the Form PTO-892 attached to Paper No. 24; hereinafter “Ansaldi”). Applicants respectfully traverse this rejection.

Claim 1 is drawn to purified uricase that is substantially free of aggregates larger than octamers, wherein greater than about 20% of the purified uricase is in the tetrameric or octameric form. Claim 34 is drawn to the purified uricase of claim 1, wherein the uricase contains no more than about 2% of aggregates larger than octamers. As the Examiner has acknowledged (*see* Paper No. 24 at page 8, second paragraph), Wu does not disclose uricases that are substantially free of aggregates larger than octamers. Hence, Wu is seriously deficient as a primary reference.

Ansaldi provides no disclosure or suggestion that would cure these deficiencies of Wu. There is no indication whatsoever that the chromatographic methods disclosed by Ansaldi would function to produce uricases that are substantially reduced in aggregates larger than octamers, wherein greater than about 20% of the purified uricase is in the tetrameric or

octameric form. First, Ansaldi does not disclose the purification of uricase *whatsoever* (see Ansaldi at col. 2, paragraphs 0019 and 0020¹). Moreover, Ansaldi discloses methods for the production of *monomeric* polypeptides, in which multimeric forms (including tetramers and octamers) of the polypeptides are undesirable and are removed from the monomers (see Ansaldi at page 1, paragraph 0006 (“Separation of protein and peptide monomers from their dimers, tetramers, and multimers presents a serious challenge to the separations scientist.”); at page 1, paragraph 0009 (“this invention provides a method for separating a polypeptide monomer from a mixture comprising dimers and/or multimers”); at page 1, paragraph 0010 (“Typical separations achieve enrichment of monomer to greater than 99.5% purity”); throughout the Examples; and in Figures 1-6). Hence, by disclosing methods that may be useful to isolate monomeric polypeptides and stating that multimeric forms of such polypeptides are undesirable, Ansaldi actually teaches *away* from purified enzyme preparations wherein greater than about 20% of the enzyme is in the tetrameric or octameric form. One of ordinary skill therefore would have found absolutely no disclosure or suggestion in Ansaldi to have modified the methods of Wu so as to produce the purified uricases of claims 1 and 34.

Thus, Wu and Ansaldi, alone or in combination, do not disclose, suggest or otherwise contemplate the claimed invention, and one of ordinary skill would not otherwise have been

¹ Applicants note that the enzyme “urokinase” is mentioned in Ansaldi in at least two locations at col. 2 (para. 0019 at line 11, and para. 0020 at line 11). However, urokinase should not be confused with *uricase* -- urokinase (EC 3.4.21.73) is a urine-derived plasminogen activator that is used as a thrombolytic agent, while uricase (EC 1.7.3.3) is used to break down uric acid as described in the present specification. Hence, urokinase and uricase are two completely different enzymes.

motivated to combine their disclosures. Accordingly, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 1 and 34 are not rendered obvious by Wu and Ansaldi, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

XI. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

(a) Claims 1 and 33 are amended as follows:

1. (Once amended) Purified urate oxidase (uricase) that is substantially free of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.

33. (Twice amended) Isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.

(b) New claims 38-41 are entered.

Size-exclusion HPLC of Recombinant Soybean Uricase
and Octamer-rich Fraction and of Candida Uricase

